A Computational Model of Oral Transmucosal Carvedilol Delivery

BEE/MAE 4530
Computer Aided Engineering —Applications to Biomedical Processes

Group 06

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1. Executive Summary

In the past few decades, there has been a rapid growth in alternative drug delivery routes. The oral cavity has gained attention as an attractive drug delivery site because it enhances drug bioavailability, allows for rapid transport to the systemic circulation, and provides a convenient delivery route. The buccal mucosa is one of the most common routes for oral drug delivery because it is relatively permeable and robust in comparison to other mucosal tissues. The buccal mucosa offers a large surface for absorption, allows for prolonged localized therapy, and avoids first-pass metabolism effects and degradation in the gastrointestinal environment.

One potential form of buccal drug therapy currently being investigated is the application of bioadhesive polymer patches to the buccal region of the mouth. Direct contact between a patch and the buccal mucosa allows a drug concentration gradient to favor diffusion into the tissue. Researchers have recently begun to use this innovative method of drug delivery with carvedilol, a non-selective β-adrenergic antagonist used to treat heart failure and high blood pressure.

Recent studies have investigated the formulation of bioadhesive patches of carvedilol. The goals of the project are to model drug delivery from a biodegradable carvedilol patch prepared with the PLGA polymer and optimize carvedilol concentration in the blood. The COMSOL Multiphysics 4.3 simulation software was used to model drug diffusion through the buccal mucosa and solve the governing equations used in our simulation. Drug diffusion was modeled using the species mass transport equation through a two-dimensional cross section including the carvedilol patch and surrounding tissue. Saliva flow over the patch and in the mucus region was modeled with one-dimensional Navier-Stokes fluid flow equations.

Concentration and flux profiles over the course of the three hour treatment confirm that carvedilol is able to diffuse from the patch and be delivered to the tissue and bloodstream. Approximately 100% of the patch is delivered within three hours. We evaluated patch efficiency using the concentration in the blood as a fraction of the initial patch concentration. The peak carvedilol concentration is reached at 1.8 hours. Drug degradation in the submucosa results in an observable reduction in carvedilol concentration in the bloodstream. Our results were validated based on cumulative drug release and peak concentration data from *in vitro* and *in vivo* studies. Since the availability of property data is limited, we performed sensitivity analysis over a range of diffusivity values and saliva flow velocities.

Multiple drugs are currently being evaluated for oral mucosal therapy, but the high costs associated with developing these drug delivery systems have limited commercial availability. Computational fluid dynamics (CFD) modeling is necessary to determine the ideal parameters and properties to maximize drug efficacy and the percentage of drug that leaves the patch in an economical and safe method. Our observations will allow carvedilol treatment to be optimized by investigating initial drug concentration in the patch and treatment time. This computer model could potentially aid the design of clinical trials testing different patch configurations and treatment times.

2. Introduction to Transmucosal Drug Delivery Modeling

The optimization of drug delivery is a critical focus of biomedical research. The investigation of alternative routes of drug delivery to maximize therapeutic efficacy is expansive, involving oral, intravenous, transdermal, inhalation and transmucosal drug delivery systems (Li et al, 2013). The latter route of drug administration involves the placement of diffusion-controlled patches, films or tablets inside the buccal (interior surface of the lips and cheeks), sublingual (underneath the tongue) or palatal (soft palate) mucosal regions of the interior oral cavity (Venkala et al, 2012).

Transmucosal drug delivery offers patients a non-invasive method of drug administration with potentially more rapid uptake. The buccal mucosal layer offers several advantages and constraints as a site of drug delivery. The literature reports that the permeability of the buccal mucosa, while less than that of the sublingual mucosa, is between 4 and 4000 times greater than that of the skin, suggesting an advantage over transdermal systems developed in previous studies (Venkala et al, 2012; Kshirsagar et al, 2012). As a more robust mucosal layer, the buccal region is able to withstand the patch application and adhesion. Additionally, the buccal mucosa exhibits a low sensitivity to irritants and allergens that may be present in the patch formulation. In the oral cavity, however, salivary flow can result in significant flushing of the drug away from the site of application (Venkala et al, 2012).

Transmucosal drug delivery is currently being investigated for a large number of medical applications, including pain control, diabetes management, and antibiotic therapy (Kumbria & Goomber, 2011). This project will focus on modeling the drug compound carvedilol, an α/β-adrenergic blocking agent which is used to treat various stages of congestive heart failure (CHF), as well as left ventricular dysfunction and hypertension (COREG Tablet, 2013). The mechanism of the drug's efficacy is fairly well-established, as β-blockers have been demonstrated to improve the function of the left ventricle of the heart. Mild to moderate dizziness, fatigue and hypotension are the most commonly reported adverse side effects of this drug compound (Vanderhoff et al, 1998). Current iterations of carvedilol therapy involve oral ingestion of tablets, with sequentially higher drug content levels of 3.125 mg, 6.25 mg, 12.5 mg and 25 mg as clinically-indicated (COREG Tablet, 2013).

This project will investigate the design of a transmucosal drug delivery system for carvedilol across the buccal region of the oral cavity. A computational model will be developed to investigate the concentration profile and flux pattern for a transmucosal carvedilol patch. The patch design incorporates a biodegradable patch polymer, often supplemented with the adhesive biocompatible polymer chitosan (Kaur & Kaur, 2012; Giannola et al, 2013). The therapeutic result, in terms of the attained peak blood plasma concentration of the drug, will be investigated and compared to animal models and available pharmacokinetic data (Arsenault et al, 2005; Nikoli et al, 2013). The effect of degradation of the drug in the blood will also be considered. Additionally, the effects of varied conditions and parameters such as the salivary fluid flow pattern and the thickness of the mucosal layers (which vary widely between different

individuals) will be computed through sensitivity analysis. Finally, this project endeavors to provide a design recommendation for an optimized transmucosal carvedilol treatment protocol by investigating the maximum cumulative drug release from the patch.

The computational model results provided clinical insight in terms of developing more effective, consistent treatment protocols. The results of this project could be translated to a variety of other long-term therapeutic drug regimens.

3. Problem Statement and Design Objectives

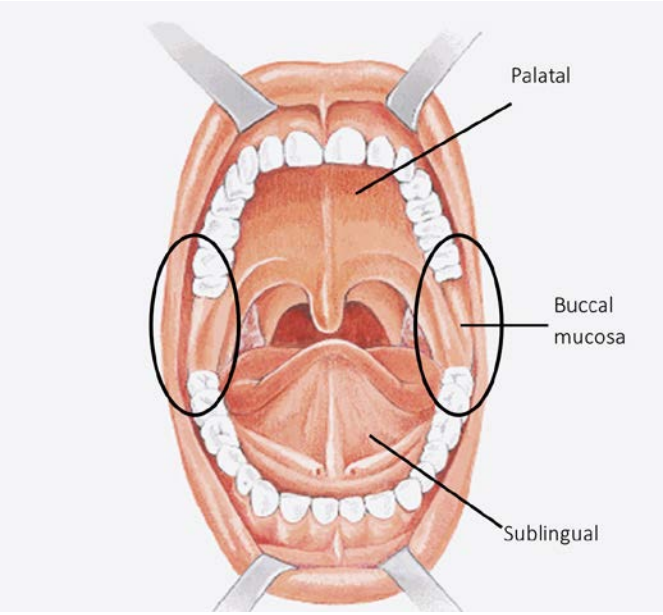
The goal of this study was to develop a computational model to investigate and optimize oral transmucosal carvedilol delivery.

Specific objectives included:

- Developing an accurate and realistic model of oral transmucosal carvedilol delivery
- Modeling the biodegradability of the patch
- Investigating drug degradation in the submucosal blood
- Conducting sensitivity analysis to determine the required precision for model input parameters
- Validating the computational model with experimental data for cumulative drug release and peak drug concentration in the blood
- Optimizing the patch efficiency using an objective function

4. Schematic

Figure 1a below shows the regions of the interior oral cavity with this model focusing on a patch placed in the buccal region. Figure 1b shows a 2D cross section of the mucus, buccal mucosa, and submucosa tissue layers. The drug diffuses from the patch through the buccal mucosa and submucosa.



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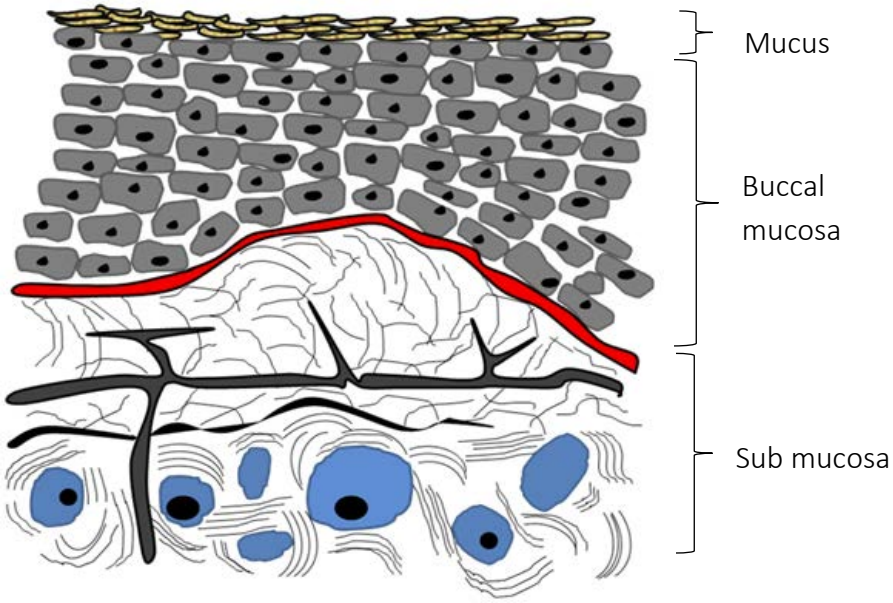
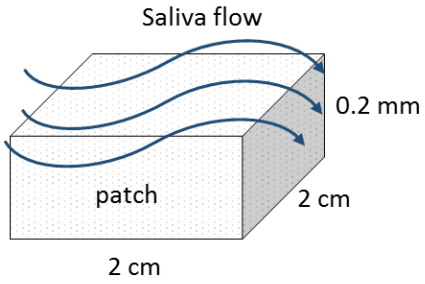


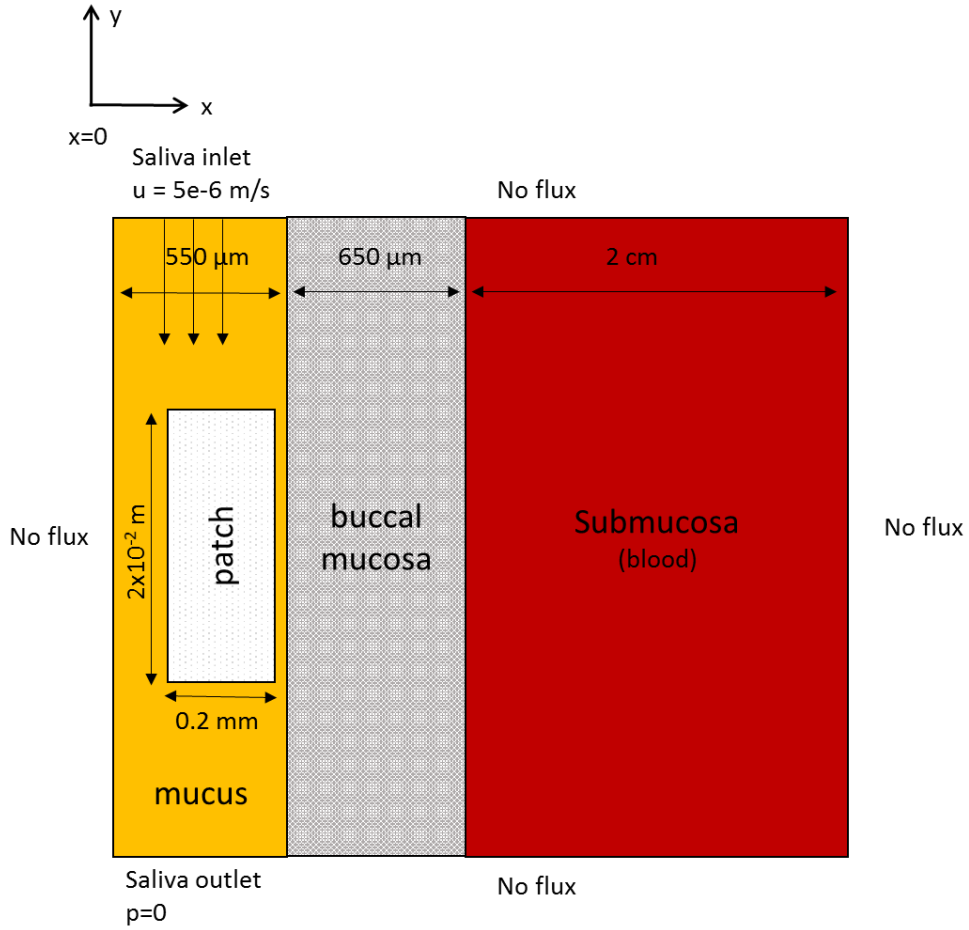
(b)

Figure 1: (a) Buccal Region of the Oral Cavity: The buccal region refers to the inner lining of the cheeks and lips. It is composed primarily of epithelial and connective tissue. (b) Structure of the buccal region of the oral cavity: The buccal region is composed of three primary layers: mucus, buccal mucosa, and submucosa. The buccal mucosa is composed of multiple layers of epithelial tissue. The sub mucosa lies beneath the buccal mucosa and consists of blood vessels and nerves.

The patch we are investigating was prepared using poly lactic-*co*-glycolic acid (PLGA), a biodegradable polymer. Figure 2a shows 1D saliva flow over this patch construct. We have simplified carvedilol diffusion through the buccal region using a 2D domain shown in Figure 2b. We are considering diffusion in the x-direction only and considering diffusion in the y-direction to be negligible because of the dimensions of the patch relative to the tissue depth.



(a)



(b)

Figure 2: Schematic of the carvedilol patch and 2D tissue cross section in our model. a) 1D saliva flow occurs over the carvedilol patch. b) Carvedilol diffusion occurs through the buccal mucosa and sub mucosa regions. Saliva flow is only present in the mucus region, which surrounds the patch. Boundary conditions for the governing equations are shown.

5. Methods

Buccal carvedilol delivery was simplified and modeled in COMSOL using the mass transport equation coupled with fluid flow physics for the saliva flow. Diffusion in the patch, mucus, buccal mucosa is modeled by the equation:

$$\frac{\partial c_A}{\partial t} + u_x \frac{\partial c_A}{\partial x} + u_y \frac{\partial c_A}{\partial y} = D_A\left(\frac{\partial^2 c_A}{\partial x^2} + \frac{\partial^2 c_A}{\partial y^2}\right) \qquad \text{[Equation 1]}$$

where c_A is the concentration of carvedilol, u_y is the saliva velocity, and D_A is the diffusivity of carvedilol in each region.

In the submucosa, there is degradation of carvedilol which is represented by the first order reaction term, R_A.

$$\frac{\partial c_A}{\partial t} + u_x \frac{\partial c_A}{\partial x} + u_y \frac{\partial c_A}{\partial y} = D_A\left(\frac{\partial^2 c_A}{\partial x^2} + \frac{\partial^2 c_A}{\partial y^2}\right) - R_A, \text{ where } R_A = -\lambda c_A \qquad \text{[Equation 2]}$$

The half-life of carvedilol in the bloodstream is reported to be seven to ten hours (Vanderhoff et al, 1998). The rate constant of carvedilol degradation in the blood was approximated using the following expression:

$$\lambda = \frac{-ln\left(\frac{1}{2}\right)}{t_{1/2}} = \frac{-ln\left(\frac{1}{2}\right)}{25200\ sec} = 0.000028\ sec^{-1} \qquad \text{[Equation 3]}$$

In order to determine the effect of saliva flow on drug delivery, a simplified Navier-Stokes equation for fluid flow was implemented. We assumed steady state saliva flow and treated the inertial and gravity terms as negligible.

$$0 = \mu\left[\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2}\right] - \frac{\partial P}{\partial x}$$
$$0 = \mu\left[\frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2}\right] - \frac{\partial P}{\partial y} \qquad \text{[Equation 4]}$$

In modeling the biodegradation of our patch, we assumed a constant rate of change in the patch thickness. We used the half-life of PLGA, 3.97 weeks, to calculate the velocity at which the patch shrinks (Vishnu, et. al. 2006).

$$\frac{0.0001m}{3.97\ weeks}\left(\frac{1\ week}{168\ hours}\right)\left(\frac{1\ hour}{3600\ s}\right) = 4.1648 \times 10^{-11}\frac{m}{s} \qquad \text{[Equation 5]}$$

Initial Conditions:

Initially, there is no carvedilol in the mucus or tissue regions because the drug is contained in the patch. The initial concentration of the carvedilol in the patch is found by dividing the mass by the volume of the patch. The patch dimensions are 2cm x 2cm x 0.2mm resulting in a patch volume of 8 x 10^{-8} m^3. We will consider carvedilol masses of 3.125mg, 31.25 mg, and 312.5 mg with the 31.25 mg carvedilol patch representing our basis for computation. The following equation was used to calculate the initial concentration of carvedilol in the patch region.

$$C_0 = \frac{m_{carvedilol}}{V_{patch}} \qquad \text{[Equation 6]}$$

Material Properties/Model Input Parameters:

The diffusivities of carvedilol in saliva, the PLGA patch, buccal mucosa, and submucosa tissue were approximated using the following equation:

$$D = \frac{(9.40\times10^{-11})(T)}{\mu M_w^{1/3}} \quad \text{(Saltzman, 2001)} \qquad \textbf{[}\text{Equation 7]}$$

Where T=310.15, M_w = molecular weight of carvedilol, and μ= viscosity of the substance.

This equation is derived from the Stokes-Einstein equation:

$$D_A = \frac{k_B T}{6\pi\mu a} \qquad \text{[Equation 8]}$$

The Stokes-Einstein equation incorporates the effects of frictional drag and temperature on the diffusivity. It is used to predict diffusion coefficients of molecules based on their molecular weights (Saltzman 2001).

6. Results

The goal of this study was to develop a computational model to investigate and optimize drug delivery from a transmucosal carvedilol patch. The following section details the results obtained from the studies performed – diffusion through the tissue layers, degradation in the submucosa blood vessels, flux into the blood, and cumulative drug release.

A. Carvedilol Diffusion in the Tissue Regions

Using a time step of 300 seconds, we modeled the release of carvedilol out of the patch over the course of the three hour treatment. The surface plots show that nearly all of the carvedilol leaves the patch within the three hour treatment.

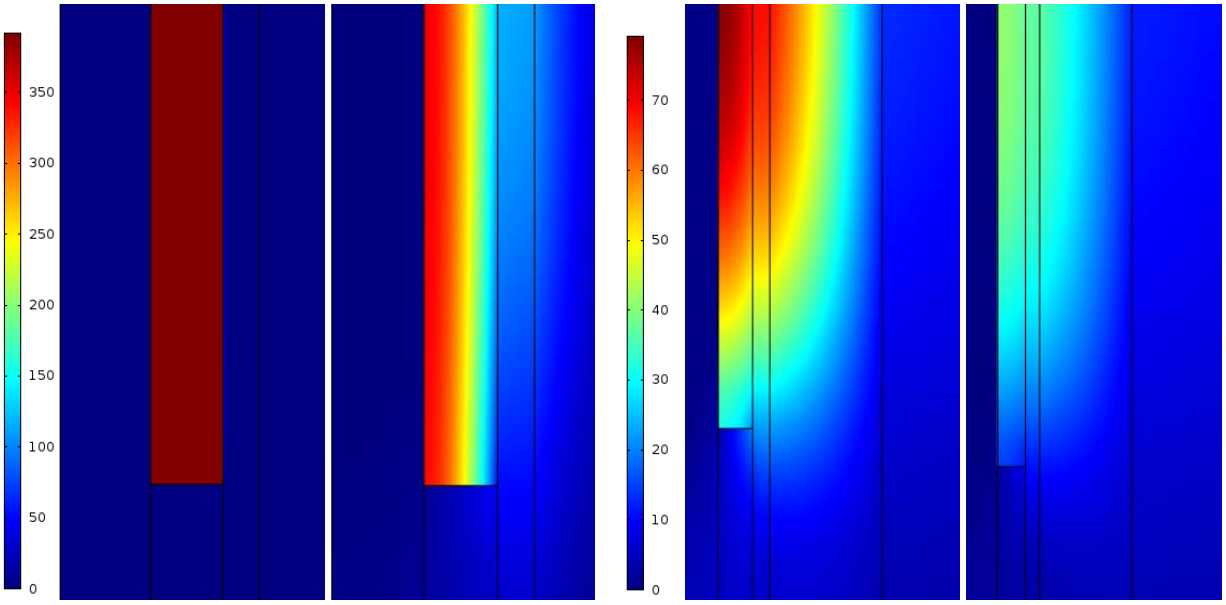


Figure 3: Surface plots of buccal carvedilol patch. Carvedilol diffusion from the patch is shown at 0 seconds, 300 seconds, 5400 seconds (1.5 hrs), and 10800 seconds (3hrs).

B. Carvedilol in the Bloodstream

Effect of degradation in the blood

Carvedilol is degraded in the submucosa; the submucosa was simplified as a uniform layer of blood due to the high density of vessels present in this tissue layer. Drug degradation in the submucosa was modeled using a first-order reaction term in the mass transport equation. Figure 4 shows the effect of degradation on the carvedilol concentration in the bloodstream. We evaluated carvedilol concentration at a point in the submucosa near the buccal mucosa and sub mucosa boundary. We confirmed that a higher maximum concentration at this point is reached without degradation.

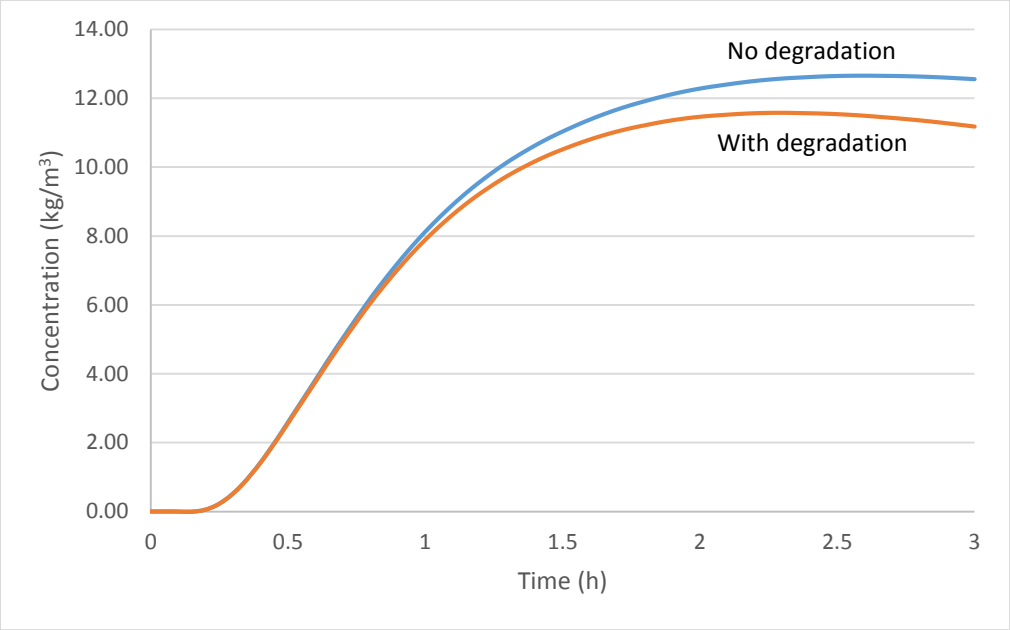


Figure 4: Effect of degradation on carvedilol concentration in the submucosa. The concentration profiles show the effect of degradation on the concentration at a specified point in the submucosa region.

Flux profile at buccal mucosa/submucosa boundary

Another objective was to determine the amount of carvedilol entering the submucosa blood vessels. First, we calculated the flux of drug into the submucosa. There is a large increase in flux at the start of treatment because of the large concentration gradient. As the drug diffuses and enters the bloodstream, the flux decreases with time because the concentration gradient decreases.

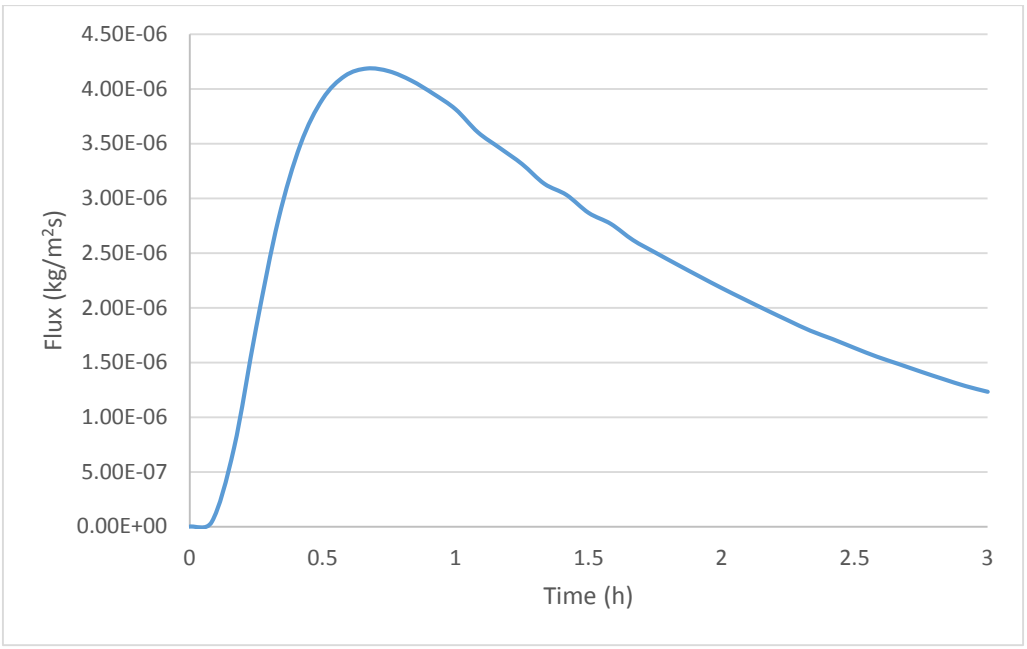


Figure 5: Flux Profile at the submucosa boundary. This figure shows the flux into the submucosa over the three hour treatment.

C. Cumulative Release Profiles

In order to determine the amount of drug that accumulates in the blood, we integrated our flux over the length of the patch to determine the mass/length of carvedilol entering the blood. As shown in Figure 6 below, the entire mass of carvedilol leaves the patch within three hours but only about 50% of the drug has entered the bloodstream. The amount of drug carried away by the mucus is minimal.

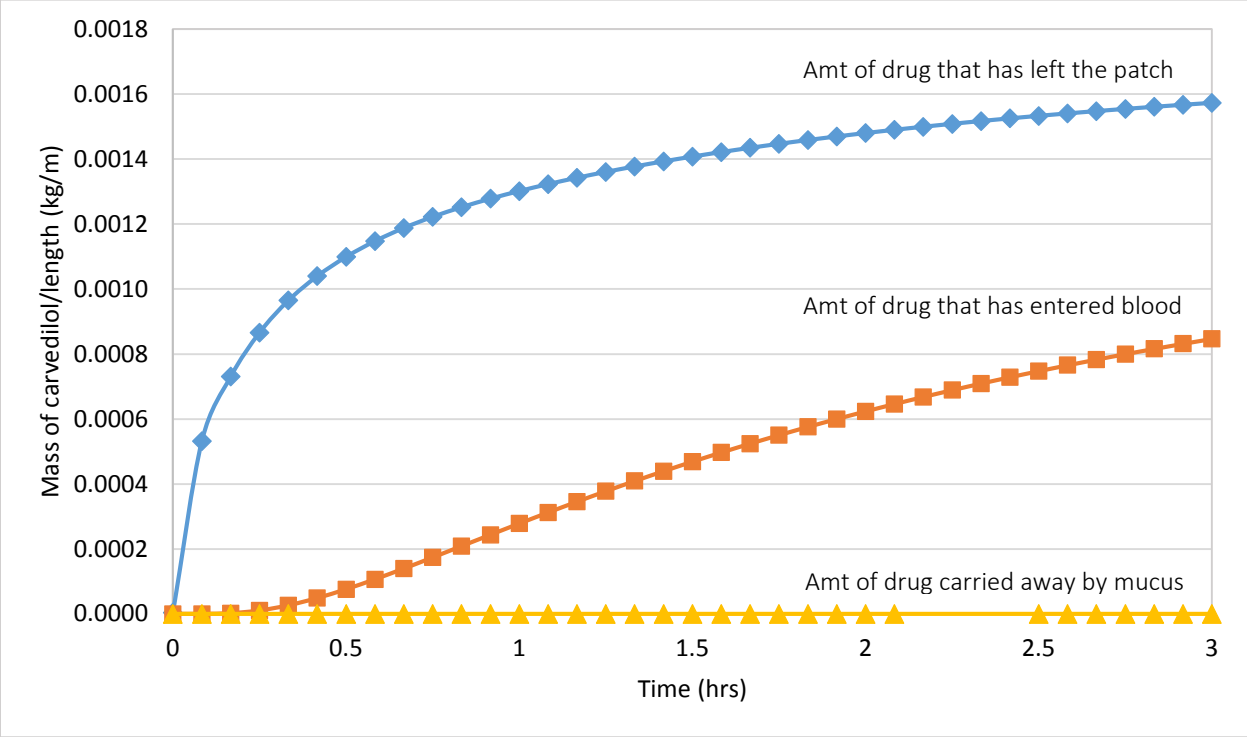


Figure 6: Cumulative drug release from the patch over time. The amount of drug that has left the patch and the amount entering the blood are shown. There is a minimal amount of drug carried away from the delivery site by saliva flow.

D. Optimization and Objective Function

In a design problem, there are numerous possible approaches to optimization. For this problem statement, the results are intended to be informative for the overall drug delivery mechanism via a transmucosal patch rather than the specific treatment with carvedilol. Therefore, rather than investigate the specific systemic concentration, we elected to develop an objective function which reflects the 'efficiency' of the patch in terms of the percentage of the initial drug concentration that reaches a particular point in the submucosa at the midpoint of the treatment. Maximizing the objective function provided in Figure 7 below represents the most efficient patch based on the initial concentration; this objective function was defined from the model of a patch of initial mass 3.125 mg. Since this objective function was derived from model data, and the model was not run for all possible multiples of the initial concentration, interpolation is required.

$$\text{Objective function: } J = \begin{cases} -50c - 2000 & 0 \leq c < 50c_i \\ -880c + 38{,}000 & 50c_i \leq c \leq 100c_i \end{cases}$$

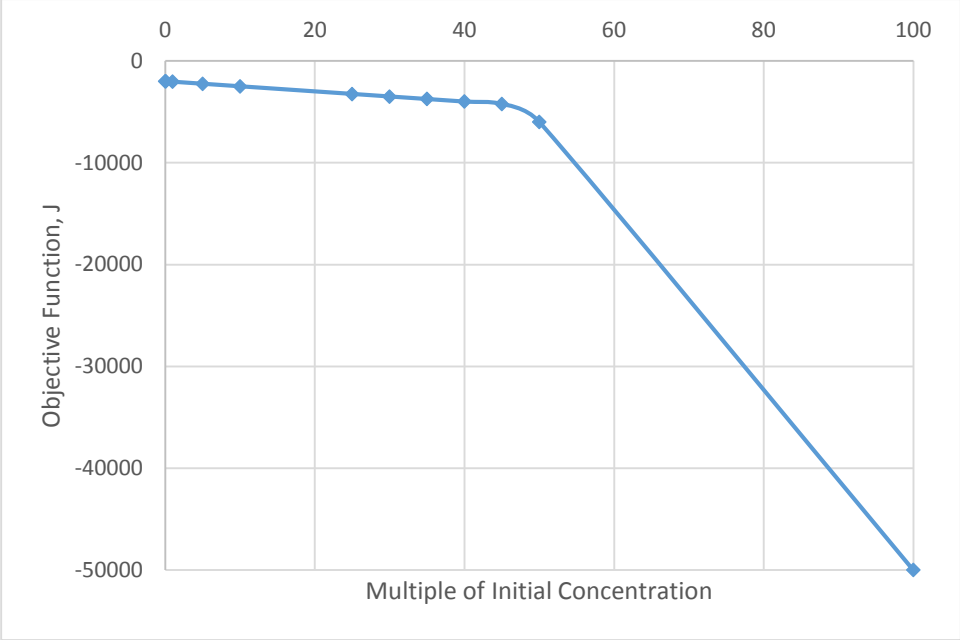


Figure 7. Objective function for optimization of patch 'efficiency'

E. Hypothetical Baseline Analysis

One of the main limitations we encountered in our model was the slow rate of degradation of the patch, given the polymer used in the initial design. Therefore, we conducted a baseline analysis of the drug delivery system with a hypothetical polymer demonstrating complete 100% degradation during the three hour treatment time. This would be beneficial for the patient because it would eliminate the need to remove the adhesive polymer from the interior surface of the cheek.

The surface plots in Figure 8 below reflect the transient carvedilol transport. As the thickness of the patch decreases with biodegradation, the mucus boundary is observed to appropriately shift.

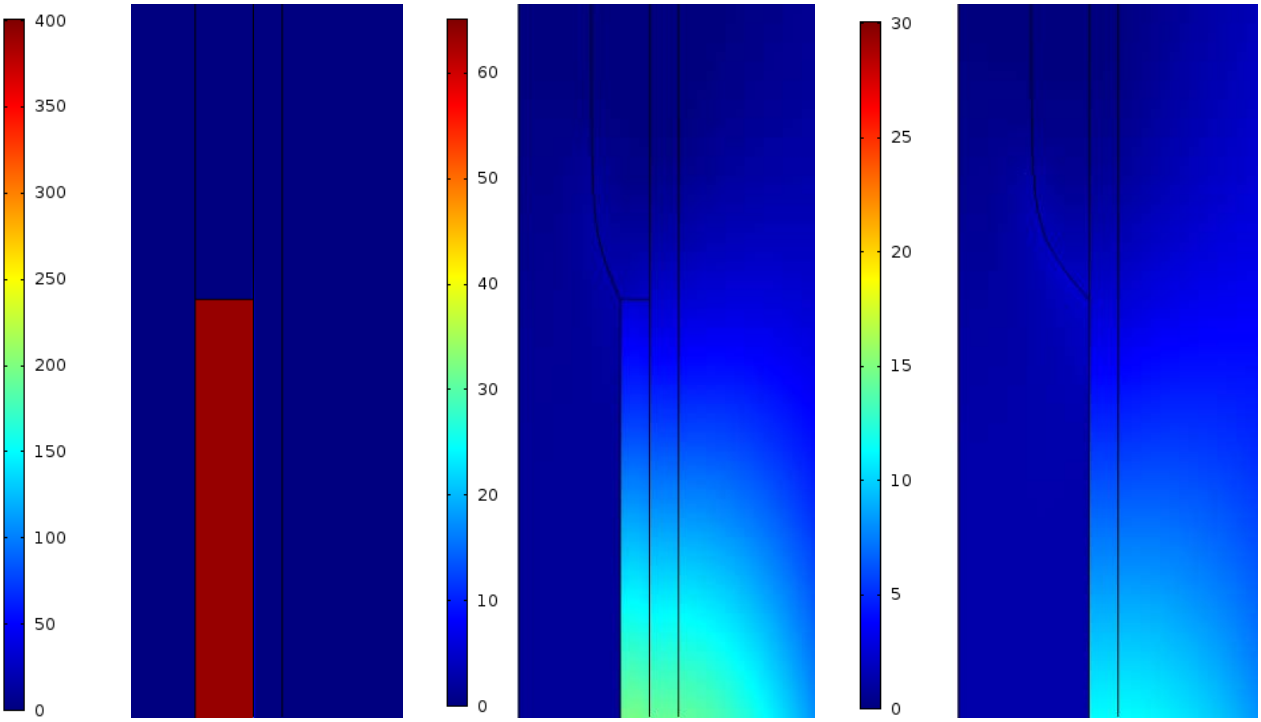


Figure 8: Surface plots of hypothetical 100% biodegradable patch. As the patch shrinks with time, it is replaced by the mucus and saliva flow layer.

7. Accuracy Check

Comparison between Cumulative Drug Release Profile and Experimental Studies

In order to validate our model, the cumulative drug release from the patch was compared to values found in literature. Since buccal carvedilol patches made using PGLA have not been well tested, we compared the drug release in our patch to that of studies using carvedilol patches containing other polymers such as HPMC and Carbopol. Cumulative drug release *in vitro* of 86.26 to 98.32% and 74.63 to 88.02% *in vivo* within 90 minutes were reported for a HPMC polymer patch (Thimmasetty, 2008).

In order to calculate the cumulative drug release in COMSOL, we first integrated the flux out of the patch over the length of the patch. Using this we were able to find the mass/length of drug exiting the patch over the course of treatment. These values were multiplied by the length of the patch and divided by the initial mass of carvedilol in the patch. We obtained a cumulative drug release profile over time and a plot of the amount of drug entering the blood. As shown in Figure 9, nearly 100% of the drug was released in three hours in the three initial carvedilol masses tested.

For the purpose of comparison and validating our studies, it is reasonable to conclude that our model produced valid results as the 90% drug release at the midpoint of treatment falls within the *in vitro* range and slightly above the *in vivo* range. There are many factors that may contribute to this difference including the polymer selection and relative masses of carvedilol and polymer in the patch. Although there are variations in our patch modeled using PLGA and the HPMC polymer tested in the study, our results indicate that the use of a biodegradable patch was effective in delivering the drug.

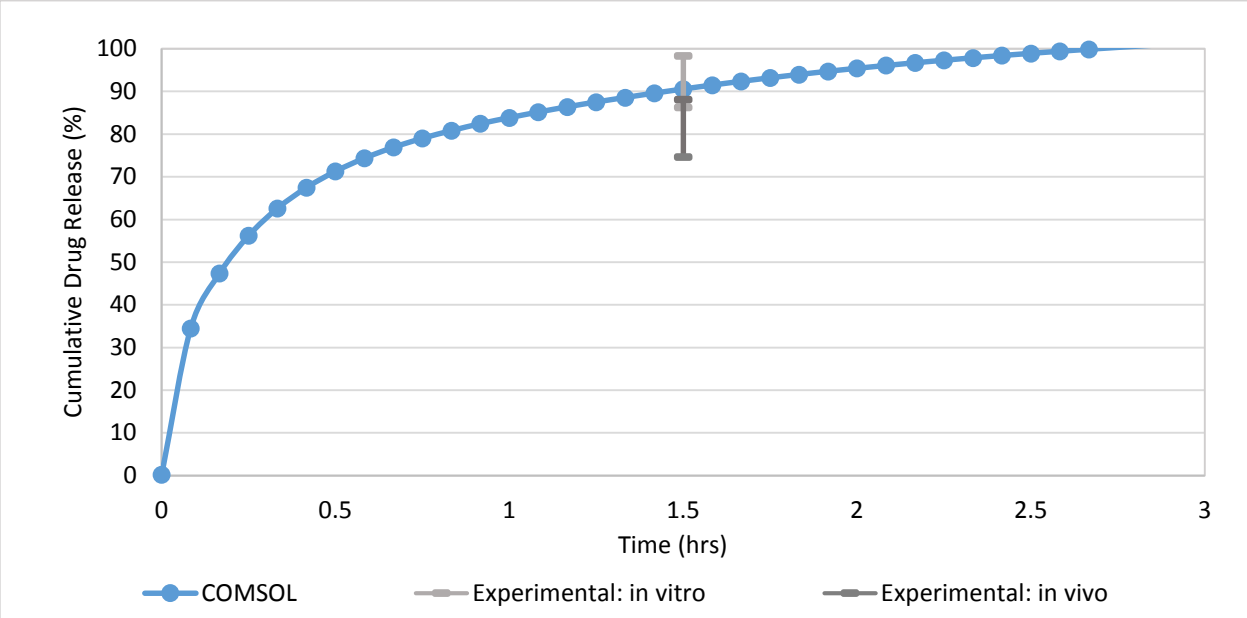


Figure 9: Cumulative Drug Release Profile. This figure shows the cumulative drug release over time from our COMSOL model patch containing an initial carvedilol mass of 3.125mg. Experimental data shows the cumulative drug release at 1.5 hours from *in vitro* and *in vivo* studies.

Analysis of Peak Carvedilol Concentration in Blood with Comparison to Experimental Studies

Another approach to validating this model involved a comparison of the peak (maximum) carvedilol concentration in the submucosal/blood region over the duration of the treatment to experimental studies in a canine model system (Arsenault et al, 2005). In our model with an initial carvedilol mass of 3.125 mg, the maximum blood concentration of 1.4655 kg/m^3 was reached at 1.83 hours, as shown in Figure 10.

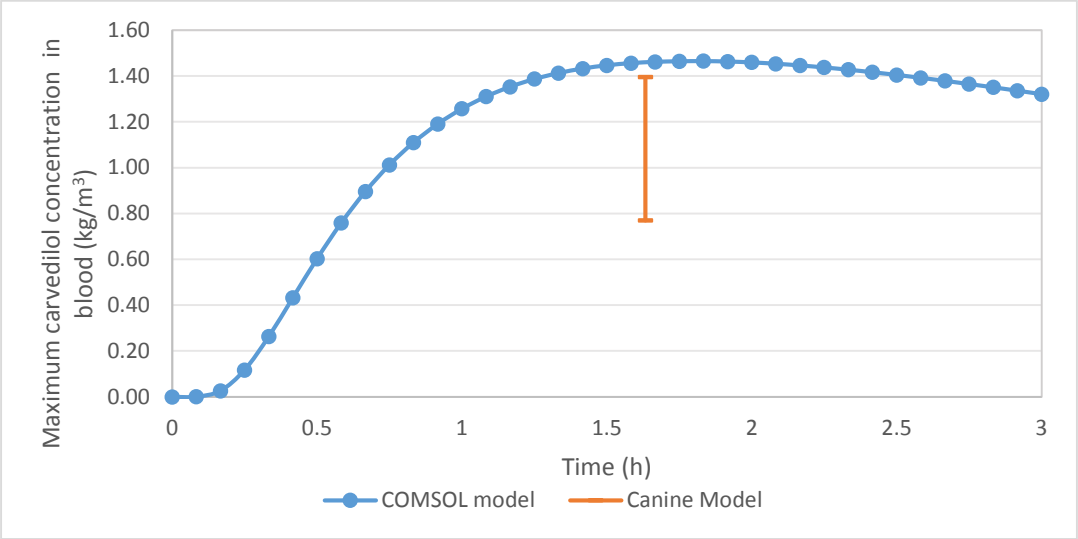


Figure 10: Peak concentration of carvedilol in the blood/submucosa region over time. With an initial patch mass of 3.125 mg carvedilol, the peak concentration is reached at 1.8 hours.

In the canine model developed by Arsenault et al, 175 µg/kg carvedilol was delivered intravenously to dogs of an average estimated mass of 25 kg. This resulted in an average drug mass of 4.375 mg. The mean peak plasma concentration was reported as 0.77 kg/m^3 (Arsenault et al, 2005).

The combination of the canine and COMSOL model results suggest some differences in the drug delivery profiles. It is important to consider that the modes of drug delivery differ; the canine model involved intravenous delivery, while our solution models transmucosal delivery via an oral patch. Nevertheless, this comparison yields two important points. First, the peak concentration was reached at approximately the same point in the treatment duration. Second, the canine model system was associated with extreme variability, with our peak concentration occurring just above the upper extreme of the canine model. On a unit initial mass basis, the transmucosal drug delivery mechanism resulted in a 2.65-fold increase in the calculated maximum carvedilol concentrations.

Overall, the discrepancies between the experimental and computed values can be attributed to the many assumptions and approximations made in modeling. The model simplified the geometry of the layers of the buccal mucosa and assumed a uniform layer of blood. Since the deviations of the model from experimental results are relatively small, it would be in the realm of possibilities to conclude that the computed results are valid.

8. Sensitivity Analysis of Various Parameters

The three main parameter types evaluated for sensitivity analysis are:

- Diffusivity of carvedilol in the mucus, patch, buccal mucosa, and submucosa: Since all the diffusivity values are approximations, diffusivity values +/- 10% of the value used were tested. The saliva was approximated to have material properties similar to that of water as there are minimal differences between the two substances. Testing the +/- 10% range accounts for differences in properties between individuals.
- Saliva flow velocity: This value varies from person to person so the +/- 10% range was applied to the saliva flow velocity to ensure that our model is more representative.
- Initial carvedilol concentration in the patch: The initial carvedilol concentration was increased and decreased by one and two orders of magnitude to assess the effect of this model parameter.

The first component of the sensitivity analysis was to assess the effect of the diffusivity in each layer on the model results. Since drug diffusivity values in different tissue layers are very difficult to obtain and can vary between individuals, it was important to determine how accurate our model parameters must be to ensure a meaningful result. A range approach to sensitivity analysis was used, which involved parametric sweeps of the different diffusivity values with the actual (approximated) parameter values as well as values + 10% and –10%. The base model values for carvedilol diffusivity are 2.1216e-11(patch), 3.9356e-10 (mucus), 5.9000e-11 (buccal mucosa) and 9.8390e-10 (blood/submucosa region). All diffusivity values are reported in m^2/s. To quantify the results of the sensitivity analysis, the concentration of carvedilol at 5400 sec, the midpoint of the treatment time, at a point very near the submucosal boundary (0.002m, 0.11m) was used as the point of analysis.

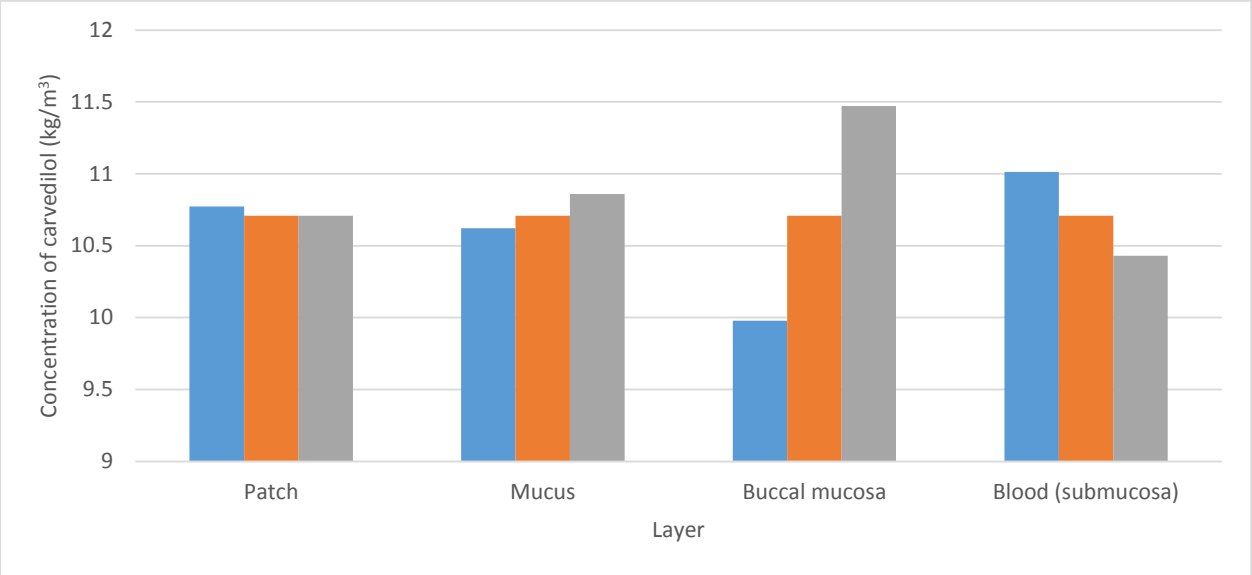


Figure 11: Sensitivity analysis for diffusivity parameters. This figure indicates that the model is sensitive to the diffusivities only in the mucus and blood/submucosal layers.

The effect of saliva flow velocity on the concentration of carvedilol at a point right outside the patch (4.8e-6m, 0.11m) at the midpoint of the treatment time was also assessed for sensitivity analysis. The base model value used for saliva flow velocity was 5.0e-6 m/s and a +/- 10% range was tested (4.5e-6 m/s and 5.5e-6 m/s respectively).

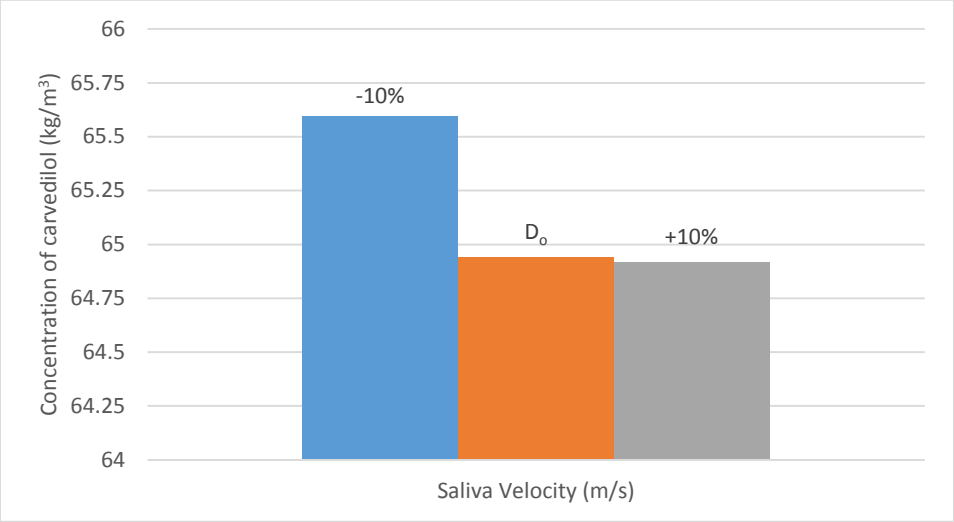


Figure 12: Sensitivity analysis for saliva flow velocity. This figure indicates that the model is slightly sensitive to velocity in the mucus layer.

Finally, the effect of the initial carvedilol concentration in the patch was investigated by varying the initial concentration by two orders of magnitude above and below the baseline value of 390.625 kg/m^3. Since this parameter directly affects the concentration profiles, the sensitivity analysis was done with respect to the concentration at the specific point (0.002, 0.11) expressed as a percentage of the initial concentration. The results in Figure 13 indicate that increasing the concentration by two orders of magnitude has the greatest effect, with other changes in the parameter negligible.

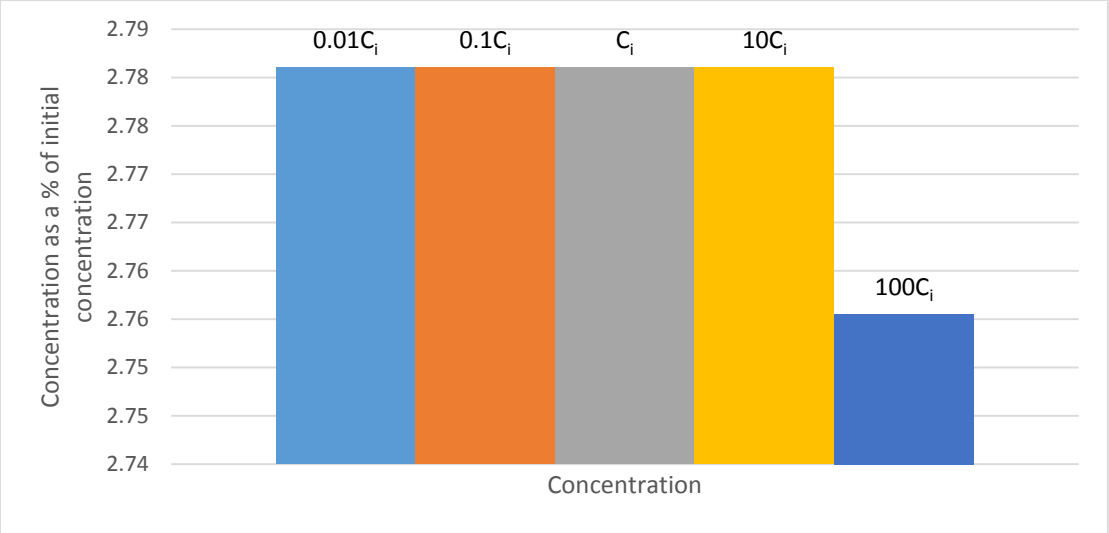


Figure 13: Sensitivity analysis for initial carvedilol concentration in the patch**.** This figure indicates that larger increases in the order of magnitude of the parameter exhibit a more pronounced effect on the carvedilol profile.

9. Conclusions and Design Recommendations

This computational model investigated the optimization of carvedilol drug delivery via an oral transmucosal patch applied to the buccal region of the interior oral cavity. The analysis centered on investigating the effect of degradation of the drug in the blood, determining the cumulative drug release profile, and assessing the peak concentration reached in the blood. The results of this modeling process are relevant both for this specific application as well as for transmucosal drug delivery systems in general.

Current research in this area involves the development of such patches for animal models. This study can provide informative results to aid in the design of targeted clinical trials with respect to parameters such as treatment duration and patch efficiency. This reflects the advantages of thorough computational modeling in reducing the need for costly and time-intensive pre-clinical trials.

A significant aspect of this project was the generation of mass per length plots which were used to calculate the amount of drug leaving the patch, the amount of drug accumulating in the blood, and the amount of drug carried away from the target delivery site by the mucus and saliva flow. While literature suggested that transmucosal drug delivery may be impeded by the flushing of drug away from the delivery site by the saliva flow, our model found this effect to be negligible for the average saliva velocity.

An additional component of this project endeavored to optimize the patch efficiency, a quantity defined as the percentage of the initial drug concentration at a particular point in the submucosal blood at the midpoint of the treatment. Comparing these values for a range of initial patch masses indicated that patches with lower initial drug masses were noticeably more efficient. Such information would be useful to pharmaceutical companies in designing a patch which is both therapeutically and economically efficient.

A key limitation of this base model was the slow rate at which the patch polymer degraded. Therefore, a preliminary analysis was conducted for a hypothetical patch construct that degrades completely during the standard treatment time of three hours. This benefits the patient by eliminating the need to remove the mucoadhesive patch at the end of the treatment. Therefore, the results of this preliminary modeling suggest that future research should focus on the design or identification of a biocompatible patch polymer which will degrade at the targeted rate.

The economic and safety constraints involved in this design process are limited. Patch materials must be biocompatible and the peak drug concentration in a patient must not exceed safe limits. Suggested areas for expanded research include investigating the effect of non-uniform salivary flow, determining the effect of individual variations in tissue layer thickness on the drug delivery, and developing a rapidly degrading patch.

10. Appendix

A. Mathematical Statement of the Problem

Governing Equations

For mass transport:

$$\frac{\partial c_A}{\partial t} + u_y \frac{\partial c_A}{\partial y} = D_A \frac{\partial^2 c_a}{\partial x^2} - R_A$$

For fluid flow (saliva):

$$0 = \frac{-\partial P}{\partial y} + \mu\left(\frac{\partial^2 v}{\partial y^2}\right)$$

Boundary Conditions and Initial Values

A. For mass transport, a no flux boundary condition was set at all outer boundaries. For fluid flow, we set the inlet velocity in the mucus layer to the average saliva velocity, $5x10^{-6}$ m/s (Watanabe, 2012). At the other end of the mucus layer, we set the outlet pressure to zero.

B. For initial conditions, we defined an initial concentration in the patch region and set the concentration in all other regions to be zero.

$$C_{0,patch} = \frac{m_{carvedilol}}{V_{patch}} = \frac{31.25\ mg}{8\ \text{x}\ 10^{-8}\ m^3} = 390.625\frac{kg}{m^3}$$

Table A1: Material properties and input parameters for mass transfer and fluid flow

Property	Value	Unit	Reference
Carvedilol molecular weight	406.5	Da	PubChem, 2014
PLGA molecular weight	150	kDa	Lu, 2000
Initial carvedilol concentration in patch	390.625	kg/m^3	N/A
Initial carvedilol concentration in mucus, buccal mucosa, submucosa	0	kg/m^3	N/A
Average saliva velocity	$5x10^{-6}$	m/s	Watanabe, 2012
Diffusivity of carvedilol in saliva	3.9356×10^{-10}	m^2/s	Datta and Rakesh, 2010
Diffusivity of carvedilol in patch	2.1216×10^{-11}	m^2/s	Sonjoy, 2011
Diffusivity of carvedilol in tissue	5.9×10^{-11}	m^2/s	Meyer, 2009
Diffusivity of carvedilol in blood	9.8390×10^{-10}	m^2/s	Meyer 2009
Carvedilol viscosity	0.01855	Pa-s	Sonjoy 2011
Saliva density	1002	kg/m^3	Mehravaran et. al., 2008
Saliva viscosity	0.01285	Pa-s	Mehravaran et. al., 2008
Blood density	1060	kg/m^3	Datta and Rakesh, 2010
Blood viscosity	0.001248	Pa-s	Klabunde, 2010

Evaluation of diffusivities

Since diffusivity values for specific drug/polymer combinations are not readily available, we calculated the carvedilol diffusivity in our PLGA patch to be 2.1216 x 10-10 m^2/s using Equation 7 and the appropriate molecular weights shown in Table A1. To evaluate our diffusivity value, we compared it to diffusivities of drugs in polymers of similar molecular

weight. Table A2 shows several patch/polymer combinations. Our calculated diffusivity value is within the range/same order of magnitude of the values found in the literature. The variability in the diffusivity values found may be due factors such as pH, hydrophobicity, polarity, and temperature.

Table A2: Diffusivity of drug/polymer combinations of similar molecular weight

Substance	**Molecular Weight (Da)**	**Polymer**	**Molecular Weight (kDa)**	**Diffusivity (m^2/s)**	**Reference**
Hydrocortisone	362	EVA	150	1.18e-11	Kydonieus, 1995
Buprenophrine	467	PLCL	162	9.98e-10	Koocheki, et. al., 2011
Ketotifen fumarate	425	HEMA	130	5.57e-10	Alonso, 2012
Timolol maleate	432	DMAA	142	6.66e-10	Alonso, 2012

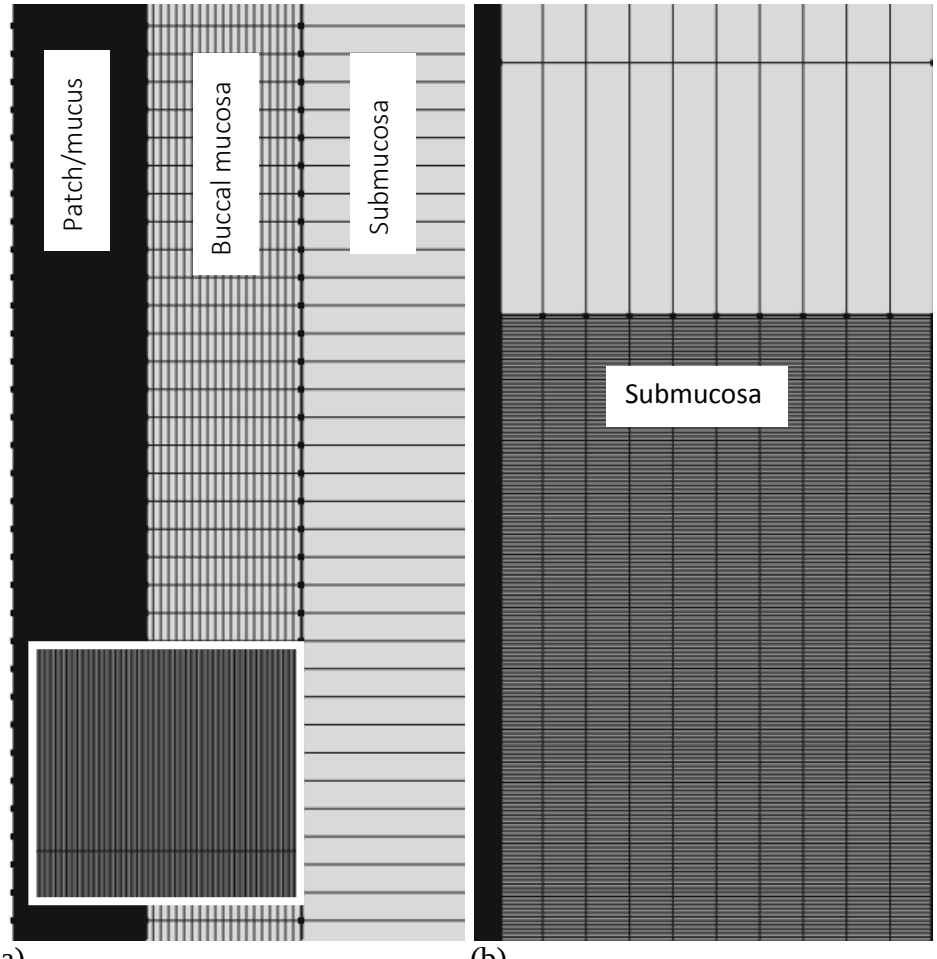
B. Solution Strategy

Solvers

The COMSOL linear systems solver direct (MUMPS and PARDISO) were used to find the complete solution of this model. The problem was a transient model solved from 0 to 10800 seconds with a time step of 300 seconds. The default values for relative and absolute tolerance, 0.01 and 0.001, were used.

Mesh Development and Convergence

We used a structured mesh due to the regular geometry of our model. A finer mesh was implemented in the mucus region directly outside of the patch where the largest concentration gradient exists. In the buccal mucosa and submucosa regions, the geometry was subdivided into regions such that the regions aligned with the patch had many more elements than those further away from the patch. This was done to reduce the computational intensity.



(a) (b)

Figure 14*:* a) Mesh for the patch/mucus, buccal mucosa, and submucosa b) Mesh for the patch/mucosa, mucosa and submucosal regions.

It was important to ensure that our solution is not dependent on the mesh chosen. Mesh convergence was assessed qualitatively for two parameters: steady state velocity and initial concentration. For steady state flow, the number of elements was increased until a smooth velocity profile around the patch edges was obtained. A smooth velocity profile was obtained with 40 mesh elements.

Velocity (Steady state flow)

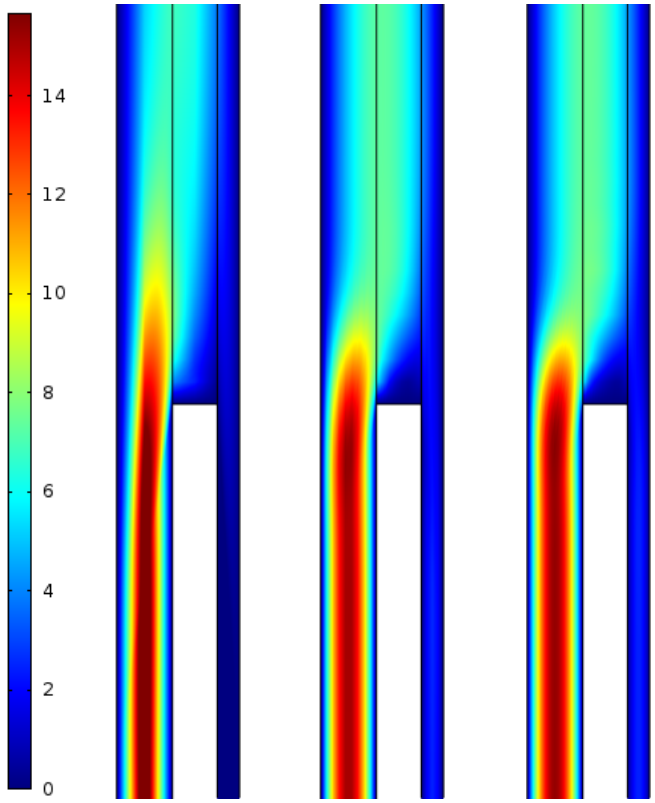


Figure 15: Surface plots of saliva velocity at 3 mesh element values. Velocity profiles are shown for a) 5, b) 20, and c) 40 elements in the vertical direction of the mucus layer.

Concentration (Mesh convergence evaluated at time t = 0)

Second, mesh convergence was evaluated for the carvedilol drug concentration at the initial time. At this time, the concentration in the patch should be equal to the initial concentration, and uniform, with no observable gradient inside the patch. The concentration in all tissue layers is initially set to 0. The surface plots of the concentration shown indicated that 800 elements for the mucus layer was sufficient.

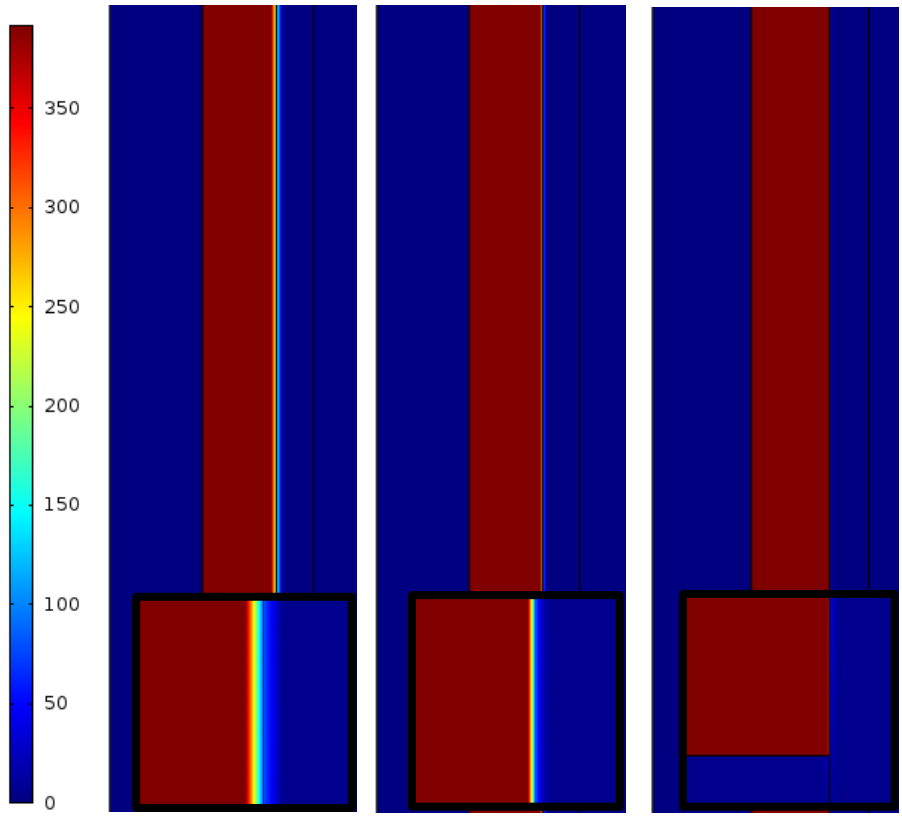


Figure 16: Surface plots of carvedilol concentration as the number of elements is increased. The plots showing carvedilol concentration at time 0 a) 40, b) 100 and c) 800 elements in the vertical direction the mucus layer. Mesh convergence occurred when the gradient on the patch/mucus boundary was eliminated and a clear distinction between the two regions could be made.

C. Additional Visuals

Sensitivity Analysis

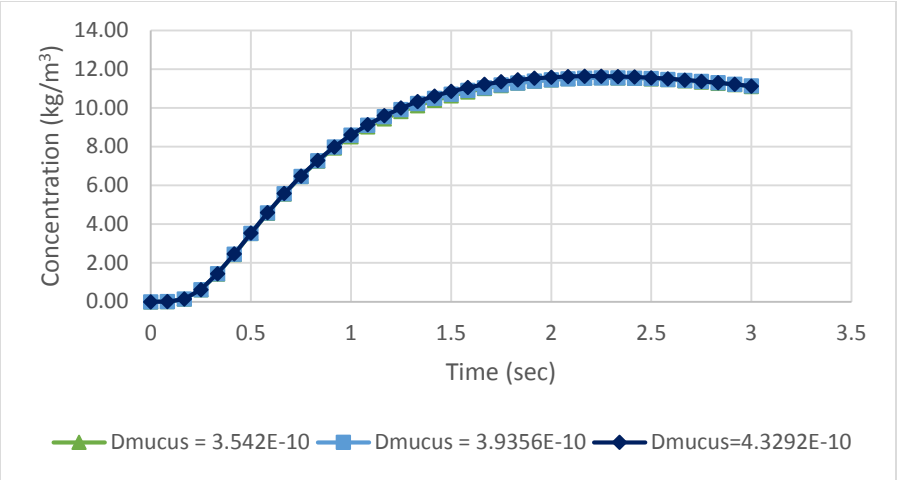


Figure 17: Sensitivity analysis with different mucus diffusivity. The graph shows that the diffusion of drug with time is insensitive to the changes in mucus diffusivity.

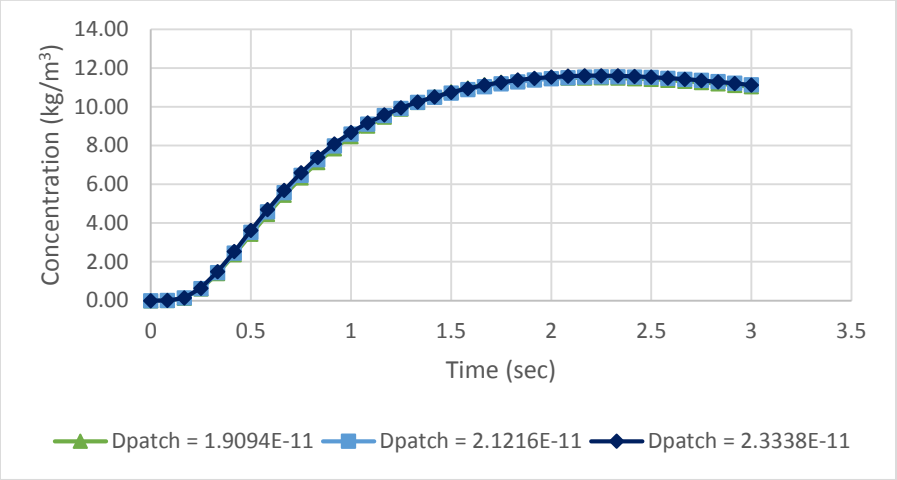


Figure 18: Sensitivity analysis with different diffusivities of the patch. The graph shows that the diffusion of the drug with time is insensitive to the changes in patch diffusivity.

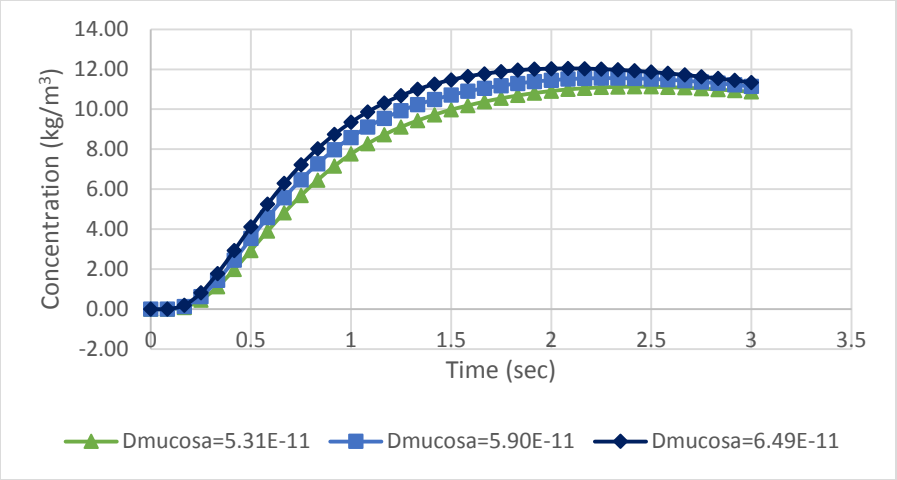


Figure 19: Sensitivity analysis with different diffusivities of the mucosa. The graph shows that the changes in mucosa diffusivity does impact the diffusion of drug with time.

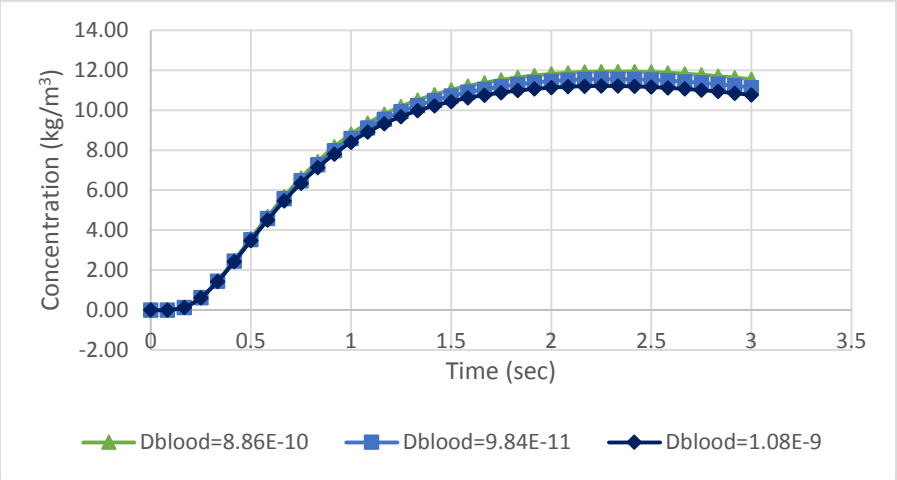


Figure 20: Sensitivity analysis with different diffusivities of the submucosa layer. The graph shows that the diffusion of the drug with time is insensitive to the changes in submucosa diffusivity.

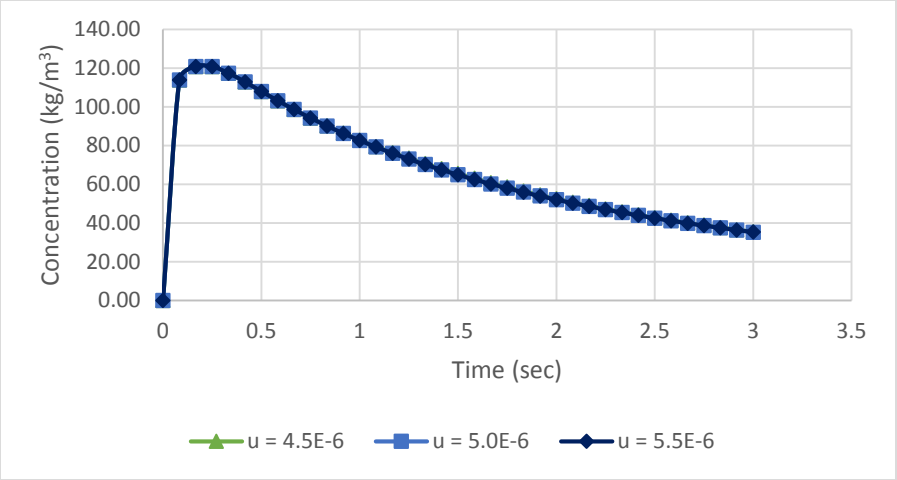


Figure 21: Sensitivity analysis with different saliva/mucus velocity. The graph shows that the diffusion of drug with time is insensitive to the changes in the saliva/mucus velocity.

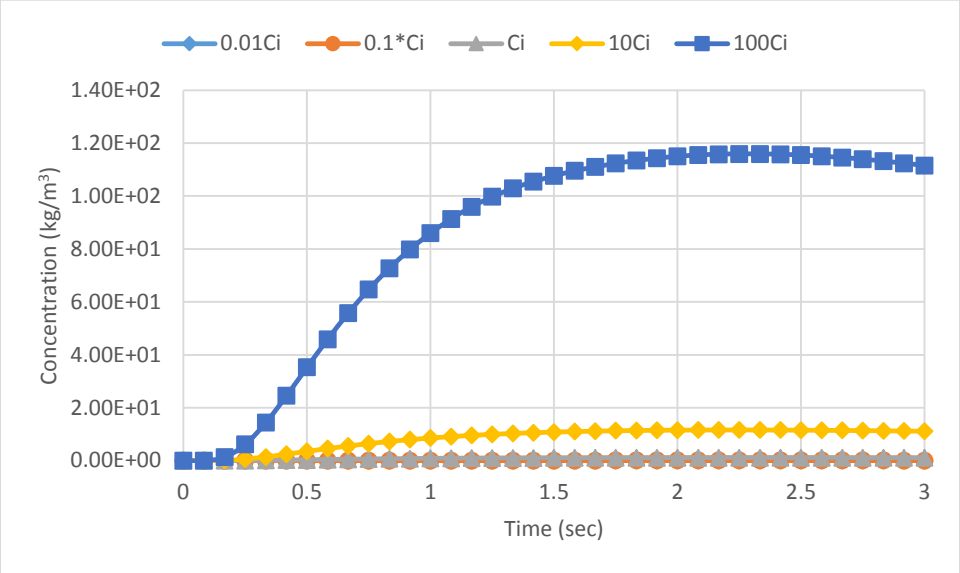


Figure 22: The graph shows the sensitivity analysis with different initial concentration of drug in the patch. The data shows that rate of drug diffusion with time is very sensitive to the initial concentration of the drug.

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